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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:	)	
	)	
Billger *et al.*	)	
	)	
Serial No.: 09/674,002	)	Group Art Unit: 1646
	)	
Filed: December 27, 2000	)	Examiner: Ruixiang Li
	)	
For: PROTEIN FORMULATIONS	)	

REPLY BRIEF UNDER 37 CFR §1.193

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This reply brief is responsive to new points of argument raised in the Examiner's Answer, dated December 19, 2003. This Reply Brief is timely filed by the deadline of **February 19, 2004.**

i. **Contrary to the Examiner's allegation, the U.S. Patent Office confirmed receipt of "Martindale" on June 20, 2003**

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Appellant had relied on Martindale during prosecution to teach that sodium chloride often causes parathyroid hormone (PTH) to precipitate from solution and, therefore, it was considered an undesirable constituent. Appellant reiterated this teaching in their Appeal Brief and also indicated that Martindale was "of record" (Appeal Brief, page 7, subsection (i)). Nevertheless, the Examiner says he only received Martindale on December 4th, after he

telephoned Appellant to request a copy (Examiner's Answer, page 11). By the Examiner's own admission, therefore, he did not have a copy of Martindale at the time he prepared and issued the Advisory Action on July 15th. This leads Appellant to believe that the Office did not properly examine all aspects of this application when Martindale was submitted originally and, hence, that prosecution was concluded prematurely.

ii. Martindale's warning that sodium chloride solutions cause PTH to precipitate from solution is a *general* teaching and does not relate to a specific formulation

In any event, the Examiner's Answer raises new points of argument with respect to Martindale. Specifically, the Examiner now contends that "Martindale's teaching is limited to his own dried parathyroid" and, therefore, that the publication "cannot be used as a basis to deny the teachings of the general art" (Examiner's Answer, pages 11 and 12). The Examiner has mischaracterized Martindale, however.

"Martindale: The Extra Pharmacopoeia" has been published by the Royal Pharmaceutical Society of Great Britain since 1883. The reference relates "reliable, unbiased and independently evaluated information on drugs and medicines" and comprises hundreds of monographs that cover "different aspects of the properties and actions" of particular drugs and compounds.

Appellant submitted page 1338 of Martindale, entitled "*Parathyroid Calcitonin and Biphosphonates*," to the Office on June 20th. In *general* terms, this monograph relates certain attributes of PTH, such as "Units" of dose, "Adverse effects and Precautions," "Absorption and Fate," "Uses and Administration," and "Preparations." The monograph also cites various reviews and publications that the skilled artisan can turn to for further information on PTH and its preparation.

In this respect, the two introductory paragraphs under section "8051-x" convey general features of PTH, *e.g.*, that it is a "single-chain polypeptide" and that it contains "84 amino acids." The section concludes by warning that "sodium chloride solutions should not be used as they often cause precipitation."

Despite this explicit warning, the Examiner states that this teaching is "limited to his own dried parathyroid," but provides no support for this statement (Examiner's Answer, page 11). This erroneous inference is compounded by the Examiner's opinion that "Martindale

does not teach, in any means, that saline cannot be used to reconstitute dried Parathyroid formulation taught by Holthuis *et al.*" (emphasis added; pages 11 and 12). To have reached such a conclusion, the Examiner had to have reasoned, paradoxically, that Martindale's "sodium chloride solution" is *not* saline, even though the Examiner defines saline as an "aqueous solution of NaCl" (page 9 of the Examiner's Answer).

Appellant considers these conclusions to be ambiguous because Martindale does not actually recommend a specific, injectable formulation for PTH. Martindale only relates various "International Standard Preparations" for parathyroid bioassays and immunoassays, *i.e.*, *not* preparations for injection. See the section entitled "Units." Martindale only notes that, for "Parathyroid Injection," PTH should be prepared in a "sterile solution in water" (emphasis added; see the section entitled "Preparations"). It is evident, therefore, that Martindale's warning against the use of sodium chloride solutions is truly a *general* teaching and is not linked to a specific, injectable formulation of PTH.

iii. Neither Holthuis nor Endo would have motivated the skilled artisan to include sodium chloride in a liquid formulation of PTH

The combination of Holthuis and Endo would not have motivated the artisan to modify either composition to arrive at the formulation recited in claims 1, 9, or 24. The Examiner seems reluctant to recognize the generality of Martindale's teaching, reasoning that "many factors" affect protein stability. He also maintains that CA 2,234,724 does not "discourage an artisan from using physiological saline (aqueous solution of NaCl) for reconstitution of PTH formulations."

In actuality, precisely the opposite is true: the '724 patent warns that sodium chloride causes PTH to dimerize and concludes that "the addition of sodium chloride has a negative effect on the storage stability." Thus, "chloride-free forms" are preferable for injection. See page 11 of the '724 patent.

The Examiner has interpreted Holthuis and Endo to exemplify art that contradicts such teachings or, at least, that renders them inconsequential. The Examiner is convinced that his interpretation better reflects the mindset of the skilled artisan prior to the present invention, and that the artisan would have similarly dismissed Martindale and the '724 patent.

Yet Holthuis, itself is silent on the detrimental effects of sodium chloride on PTH in solution, and cites Martindale, which informs against the incorporation of salt. Furthermore, it is inappropriate to generalize, as the Examiner has done, the effect(s) of salt on a solid versus a liquid PTH formulation. That is, it is improper to superimpose Endo's teachings regarding lyophilized PTH on Holthuis' composition to arrive at Appellant's claimed liquid formulation.

To counter, the Examiner contends that "there is no teaching that NaCl *cannot* be used to reconstitute the dried formulation taught by Holthuis *et al.* (emphasis added; Examiner's Answer, page 13). On its face, this logic is fatally flawed. The absence of a teaching cannot possibly validate the notion of *carte blanche* motivation to have co-formulated any desired compound, simply because the reference does not forewarn explicitly against the inclusion of that compound. Informed by Holthuis, the artisan would have had to have been motivated, somehow, to include sodium chloride in liquid PTH. Yet neither Holthuis nor Endo encourages such an action; instead, Martindale and the '724 patent actually counsel against including sodium chloride.

iv. Selsted teaches formulating indolicidin peptides with various compounds, such as EDTA and, therefore, the skilled artisan would not have been motivated to add EDTA alone to liquid PTH without indolicidin

The antimicrobial agent in Selsted (U.S. patent No. 5,547,939) is a tryptophan-rich, indolicidin protein analog, *not* simply EDTA alone, as the Examiner contends. Selsted teaches that "other compounds can also be administered in conjunction with indolicidin peptides" (column 7, lines 13-15), such as the combination of an antimicrobial indolicidin and EDTA. Selsted does not teach or suggest formulating a drug with only EDTA and no indolicidin. Accordingly, Selsted says nothing about selecting appropriate concentrations or amounts of EDTA for formulation with a highly concentrated PTH liquid.

At the very most, the skilled artisan would likely have been motivated to add indolicidin *and* EDTA to Holthuis' or Endo's PTH formulations, but would not have been motivated to add EDTA alone. Accordingly, present claims 20 and 25 are not rendered obvious.

v. **The skilled person would know what the term "stable" means without the need for a "clear definition"**

The skilled person would readily understand "stable," in the context of a therapeutic formulation, to mean that the environment of the protein or drug, prevents the protein or drug from, for example, precipitating, degrading, or losing activity. Contrary to the Examiner's note, Appellant does not have to provide a "clear definition" for the term in the specification.

It *is* clear from the specification that Appellant contemplated a "stable" PTH formulation. Thus, Appellant discussed various aspects of PTH stability under the subsections and Table legends entitled "Effect of protein concentration on PTH stability," "pH Stability," "Effect of ionic strength on PTH stability," "Effect of tonicity modifiers on PTH stability," "Effect of preservatives on PTH stability," "PTH stability in lyophilized formulations" and "PTH stability in liquid formulations." See pages 8-11, and Tables 1 and 2 at pages 13 and 14. Accordingly, there is no ambiguity regarding "stable" in claim 1.

CONCLUSION

For these reasons, and for those propounded in Appellants' brief on appeal, the Board is requested to reverse the final rejection and send the application to issuance.

Respectfully submitted,

Date: 19 February 2004

By: S. A. Bent

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Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

Title: PROTEIN FORMULATIONS
Inventor(s): Martin BILLGER et al. Dkt. No. 016777/0436
Appl. No.: 09/674,002 SABE (06/20/03)

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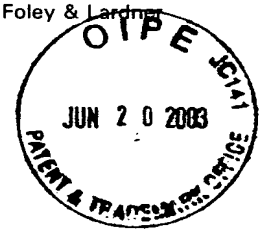
Respectfully,
Foley & Lardner

DATE DUE: June 24, 2003 **SABE/VSM/daf**



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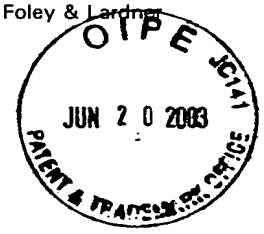

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